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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/801,078	03/15/2004	Krzysztof Palczewski	029060-000200US	9475

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EXAMINER	
HUANG, GIGI GEORGIANA	
ART UNIT	PAPER NUMBER
1617	
MAIL DATE	DELIVERY MODE
02/23/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	Application No.	Applicant(s)	
	10/801,078	PALCZEWSKI ET AL.	
	Examiner	Art Unit	
	GIGI HUANG	1617	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 04 February 2011 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).

5. ☐ Applicant's reply has overcome the following rejection(s): _____.

6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *52 and 54-62*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).

9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).

10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☐ The request for reconsideration has been considered but does NOT place the application in condition for allowance because:
    See Continuation Sheet.

12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____

13. ☐ Other: _____.

/Zohreh A Fay/
Primary Examiner, Art Unit 1627

Continuation of 11. does NOT place the application in condition for allowance because: Applicant's arguments are centered on the assertion that Chapple's reference to the use of 9-cis retinal a a chemical chaperone to stabile the mutant P23H rhodopsin citing the work of Saliba, does not produce a funcitnal rhodopsin analogue as it does allow the mutant P23H when incubanted with the 9-cis retinal produced a mature form of the protein in the soluble fraction suggesting efficient transit throgut the Golgi but does nott lead to a significant decrease in the formation of aggresomes. Applicnat also asserts that as a result, Chapple does not indicate a means to treat the P23H mutation and 9-cis retinal would not alter the affected the occurance of aggresomes.This is fully considered but not persuasive. The teachings of Chapple are being taken out of context and the reference to the work of Saliba is also being taken out of context.

Chapple is very clear. Chapple teaches that to address rhodopsin folding, one can use pharmacological agents to manipulate chaperone expression/function for retinitis pigmentosa, and one can also use the protein folding by using chemical chaperones or stabilise the protein structures with ligands. Chapple supports the statement that one can manipulate/stabilize the protein (mutant) as the use of retinals have been shown to improve folding of mutant opsin. Chapple cites that previous works support this citing the addition of 11-cis-retinal and 9-cis retinal improving folding of T17M mutant opsin (refering to the work of Sung), that 9-cis retinal when cultured with P23H mutant opsin improved the amount of opsin that reached the plasma membrane (improved stability of the protein to allow transport (refering to the work of Saliba), and that modified retinoids like 11-cis-7 ring retinal had improved the folding of P23H mutant rhodopsin. Chapple then clearly states that "These data suggest that retinoids may be used as 'chemical' chaperones that can stabilise the folding of mutant opsins shifting the equilibrium away from aggregation and towards functional protein." Chapple then states that the clinical trial would be expected to be better if focused on patients with the misfolding mutations and further investigation to stabilise and promote the correct folding of the mutant rhodopsin through these two modalities: chemical chaperones and molecular chaperones can be novel therapies for these diseases. This is a clear teaching. The references address folding such as that in the P23H mutation and that 9-cis retinal was useful for transport and that modification of a retinoid like 11-cis 7-ring retinal also allowed for improved folding of the same rhodopsin wherein with the clear statement and suggestion by Chapple to explore retinals for these mutant proteins in retinits pigmentosa, it would be obvious to one of skill in the art in view of Asato to use other retinals such as the modified 9-cis retinal that is functionally equivalent such as the 9-cis-10F-retinal with a reasonable expectation of success of addressing the folding and stabilization of the mutant P23H protein. As for the assertion to Saliba for the aggregate, as addressed above, the reference of the work of Saliba by Chapple is clearly directed that the 9-cis retinal was able to stabilize the P23H protein to transport across the plasma membrane. It was not directed to the aggregate, it was directed to the ability of retinals like 9-cis to be able to manipulate and stability the folding of mutant protein. It is noted to Applicant that Saliba addresses that the 9-cis was able to bind and stabilize the protein to cross the plasma membrane but could not disassociate upon crossing the membrane, but Chapple states that the utility of the retinals like 9-cis and modified retinal for these conditioins like P23H and for human patient being promising. Applicant should be aware that their own argument for non-enablement for forms of 9-cis retinals could be seen as an issue of enablement for the instantly claimed retinal.

In regards to the argument that there is not reasonable expectation of success in how analogues bind to mutant opsin compared to wil-type is not persuasive as this is not substantiated by evidence. It is well within the skill in the art and with reasonable expectation of success that when two 9-cis retinal forms can both bind to form functional pigments with wild-type, and one of the forms can bind to the mutant type (P23H), the other 9-cis form has a reasonable expectation to bind to the mutant opsin absent evidence to the contrary.

The rejections are maintained.